The claims have been rewritten to more clearly define Applicants' invention and to overcome the rejections of the claims under §112. The application claims are now directed to methods of detecting a translocation associated with chromosomal abnormalities, such as cancers and more specifically CML, in a sample. Support for these claims may be found in the instant application and in the applications from which priority is claimed. For example, support may be found in the instant application at the very least at page 19, line 3 - page 20, line 17; page 22, line 23 - page 23, line 16; page 37, line 4 - page 38, line 21; page 46, line 23 - page 47, line 2; page 47, line 9 - page 49, line 13; page 63, line 17 - page 64, line 5; page 72, line 4 - page 74, line 17; and page 113, lines 14-21; page 114, lines 7-25; page 115, line 5 - page 123, line 25; and Figures 8-12.

Support may also be found in U.S. Application No. 627,707, now U.S. Patent No. 5,447,841, from which priority is claimed, at the very least at page 8, lines 14-22; page 10, lines 9-24; page 12, lines 1-15; page 13, line 1 - page 15, line 8; page 20, line 10 - page 21, line 4; page 23, line 23 - page 26, line 21; and Section IV. No new matter has been added by these new claims.

The title has been amended in view of the Examiner's objection.

Claims 10-12, 17-19, 51-53 and 127-130 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. This rejection is now moot in view of the instant amendment. For CML, the claims now of record recite detection of the BCR-ABL translocation associated with CML. More generic claims directed to detection of translocations associated with chromosomal abnormalities have also



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been added, wherein probes complementary to nucleic acid segments that flank and/or extend partially or fully across breakpoint regions known to be associated with genetic translocations are employed.

Based upon the teachings of the specification, one skilled in the art would be able to stain targeted chromosomal DNA to detect in an interphase cell one or more genetic translocations identified with chromosomal abnormalities. While the specification describes in detail detection of the BCR-ABL fusion for diagnosis of CML, this same method could be used by the skilled artisan to detect any known genetic translocation identified as being indicative of a chromosomal abnormality. Other translocations are clearly known in the art.

In this regard, enclosed is a copy of a Review Article by T. Rabbitts from *Nature*, 372:143-149 (1994). Please note Table 1, which lists numerous translocations correlated to blood based cancers and a shorter list of those for solid tumors. This table supports the argument that the method described in the application to detect translocations in an interphase cell could be used to detect other blood based cancers and solid tumors. Further, please note in Table 1 under (b) that translocation t(3; 21)(q26; q22) is indicative of both CML and Myelodysplasia, a different blood based cancer. Thus, *exactly the same* multiple probe method of claims 133-139 would be used to detect the translocation indicative of Myelodysplasia.

Moreover, the instant specification describes in several places the general utility of the method of the invention to detect translocations. *See,* for example, page 19,



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lines 3-18; page 38, lines 8-21; and page 113, lines 14-21, which describes the chromosome 8 and 14 translocation involved in Burkitts lymphoma (this translocation is also listed in Table 1 of Rabbitts).

The claims now of record are thus clearly enabled by the specification. Withdrawal of the rejection is thus believed to be in order.

Claims 10-19, 51-53 and 127-130 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection is believed to be moot in view of the new claims now of record, and cancellation of the prior claims.

Claims 11, 13-15 and 53 have been rejected under 35 U.S.C. §112, fourth paragraph, as allegedly being of improper dependent form. This rejection is now moot in view of the cancellation of these claims.

Claims 10-15, 17-19, 53, 129 and 130 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yunis et al. Claims 10-15, 17-19, 53, 128 and 130 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Olsen et al. Claims 10, 11, 17-19, 51 and 53 were further rejected under 35 U.S.C. §102(e) or, alternatively, under 35 U.S.C. §103 as being unpatentable over Weissman et al. Claims 10, 11, 17-19, 51, 53, 128 and 130 were also rejected under 35 U.S.C. §103 as being unpatentable over Weissman et al in view of Sealey et al. These rejections, as applied to the claims now of record, are respectfully traversed.



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The claims now of record recite a method of staining target chromosomal DNA to detect in an interphase cell one or more genetic translocations identified with chromosomal abnormalities, said method comprising:

(a) providing a heterogeneous mixture of two or more nucleic acid probes having a combined complexity of at least 40 kb, which probes contain nucleic acid segments which are substantially complementary to nucleic acid segments that flank and/or extend partially or fully across breakpoint regions known to be associated with genetic translocations, wherein each probe comprises a distinct fluorescent label;
(b) reacting the heterogeneous mixture with the targeted chromosomal DNA by in situ hybridization; and
(c) observing the proximity or overlap of the regions stained by each probe, to determine whether said translocation is present in the interphase cell.

Other embodiments of the invention include:

(1) a method of distinguishing normal and malignant cells comprising staining target chromosomal DNA to detect genetic translocations identified with chromosomal abnormalities of malignant cells;

(2) a method of determining prognosis for a patient and/or determining the effectiveness of a therapy comprising staining target chromosomal DNA to detect genetic translocations identified with chromosomal abnormalities of malignant cells; and

(3) a method of staining target chromosomal DNA to detect genetic translocations identified with chromosomal abnormalities, wherein the distinct fluorescent label is added to the nucleic acid after the heterogeneous probe mixture is reacted with the targeted chromosomal DNA by in situ hybridization.



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None of the cited references, either alone or in combination, teaches a method of staining target interphase chromosomal DNA as now claimed by applicants. The cited references also fail to disclose or suggest a method of staining target chromosomal DNA to detect in an interphase cell one or more genetic translocations identified with chromosomal abnormalities.

Withdrawal of these rejections are thus respectfully requested and believed to be in order.

Claims 10-12 and 127-130 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 5,447,841. This rejection now moot in view of the instant amendment. Withdrawal of this rejection is thus respectfully requested.

The disclosure was objected to in view of various informalities. These informalities helpfully noted by the Examiner have been corrected. Withdrawal of the objection is thus believed to be in order.

Applicants note with appreciation the indication by the Examiner that claims 16, 51 and 52 are allowable over the prior art. Claims of similar scope directed to detection of CML using the BCR and ABL probes are now pending as claims 134-140. The Examiner further noted that the identified claims were allowable over the prior art because "hybridization detection via different probe labeling . . . is neither taught nor suggested by the prior art of record." Applicants note that all of the claims now of record recite two or more probes "wherein each probe comprises a distinct fluorescent label."



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Claims 146-148 are similar in scope to claims 51 and 52, and should thus also be found allowable over the prior art.

Further and favorable action in the form of a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this response, or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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